

Raised urinary glucocorticoid and adrenal androgen precursors in the urine of young hypertensive patients: possible evidence for partial glucocorticoid resistance

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Abstract

Objective—To evaluate urinary glucocorticoid excretion profiles in a cohort of recently diagnosed young hypertensive patients.

Methods—After excluding patients with secondary causes, 60 individuals with premature hypertension were recruited (diagnosed by ambulatory blood pressure monitoring before the age of 36 years). In addition, 30 older hypertensive controls (age of onset > 36 years, “middle aged hypertensive controls”), and 30 normal controls (age matched to the young hypertensive group) were studied. All provided 24 hour urine collections for mass spectrometry for total cortisol metabolites and total androgen metabolites by gas chromatography.

Results—Among male patients, those with premature hypertension had higher total urinary excretion of cortisol metabolites (mean (SD), 13 332 (6472) µg/day) than age matched normal controls (7270 (1788) µg/day; $p = 0.00001$) or middle aged hypertensive controls (8315 (3565) µg/day; $p = 0.002$). A similar increase was seen among the female patients, although the absolute concentrations were lower. There was no significant difference between middle aged hypertensive patients and normal controls. Urinary total androgen excretion profiles in female patients also showed an unusual increase in the premature hypertension group (2958 (1672) µg/day) compared with the other groups (middle aged hypertensive controls, 1373 (748) µg/day, $p = 0.0003$; normal controls, 1687 (636) µg/day, $p = 0.002$). In all subjects, serum sodium and creatinine concentrations were within the normal range; serum potassium concentrations were found to be low before the start of treatment.

Conclusions—Individuals presenting with premature hypertension have an abnormally high excretion of glucocorticoid metabolites in the urine. While the mechanism remains uncertain, these findings are compatible with partial resistance of the glucocorticoid receptors, with a compensatory increase in cortisol and androgen metabolites. The mineralocorticoid effects of the latter (sodium and water retention) may contribute to an abnormally high blood pressure and may have implications for targeted selection of first line treatment in young hypertensive patients. (Heart 2001;86:139–144)

Keywords: premature hypertension; glucocorticoid resistance; cortisol metabolites; glucocorticoid receptor resistance

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Hypertension is common worldwide and confers an increased risk of stroke, myocardial infarction, and renal failure. It may affect half the population over the age of 60 in developed countries.¹ In only a small minority of cases is a clear cause found, such as chronic renal disease (2%), renovascular disease (2%), primary aldosteronism (1%), Cushing's syndrome (0.5%), pheochromocytoma (0.2%), oral contraceptives (0.2%), and coarctation of the aorta (0.2%).^{2–4} The vast majority of patients are therefore given the diagnosis of essential hypertension.

Among hypertensive patients referred to specialist centres, 10% are referred for refractory hypertension and there is increased representation of young patients.⁵ Results of the Four corner study hinted that abnormalities of cortisol metabolites may have particular importance in hypertension in young patients.⁶

Glucocorticoids are important in maintaining vital haemodynamic mechanisms in the body. Cortisol has mineralocorticoid-like effects^{7–11} and may have a role in the regulation

of systemic arterial blood pressure. It could be involved in the pathogenesis of hypertension, as previously suggested by studies on humans^{12–15} and animals.^{12–16} Some abnormalities of cortisol metabolism are well recognised (for example, Cushing's disease) but there are other less well known conditions where glucocorticoid abnormalities can cause hypertension.^{17–19} Milder abnormalities of glucocorticoid production and excretion rates may be more common in hypertensive subjects, particularly those who present when they are young. Our aim in this

Table 1 Antihypertensive drug treatment in the hypertensive groups

Drug treatment	Premature hypertension	Hypertensive controls
β Blocker	26 (43%)	14 (46%)
Diuretics	12 (20%)	9 (30%)
Calcium channel blocker	32 (53%)	13 (43%)
ACE inhibitors	41 (68%)	22 (73%)
Angiotensin II receptor blockers	22 (36%)	15 (50%)
α Blocker	8 (13%)	5 (16%)

Values are numbers of patients taking a particular drug (% of total number of patients).

ACE, angiotensin converting enzyme.

Table 2 Patient characteristics

	Normal controls	p Value (A)	Premature hypertensive	p Value (B)	Middle aged hypertensive
<i>Male subjects</i>					
Age (years)	31.1 (4.0)	0.07	35.5 (10.4)	0.02	46.4 (7.0)
Age at presentation (years)			28.0 (7.1)	< 0.0001	42.5 (4.8)
n	14		34		17
BMI (kg/m ²)	25.0 (1.2)	0.2	25.6 (3.4)	0.85	25.9 (2.8)
Heart rate (beats/min)	76 (4)	0.65	77 (6)	0.9	77 (19)
Systolic BP (clinic)	124	< 0.0001	158	0.004	181
Diastolic BP (clinic)	76	0.002	98	0.03	112
Hb (g/dl)	14.4 (0.5)	0.92	14.4 (0.6)	0.35	14.0 (0.6)
<i>Female subjects</i>					
Age (years)	30.5 (3.9)	0.1	32.3 (7.5)	< 0.0001	51.8 (7.8)
Age at presentation (years)			27.5 (5.6)	< 0.0001	48.2 (8.0)
n	16		26		13
BMI (kg/m ²)	26.7 (6.2)	0.7	27.3 (5.4)	0.34	30.7 (8.0)
Heart rate (beats/min)	76 (6)	0.53	78 (7)	0.62	79 (4)
Systolic BP (clinic)	118	0.003	146	0.29	158
Diastolic BP (clinic)	78	0.0001	96	0.84	96
Hb (g/dl)	13.7 (1.1)	0.16	13.3 (0.4)	0.09	12.1 (1.7)

Values are mean (SD).

(A), p value between normal controls and premature hypertensive patients; (B), p value between premature hypertensive and middle aged hypertensive patients.

BMI, body mass index; BP, blood pressure; Hb, haemoglobin.

study was to examine the adrenal steroid component in patients presenting with hypertension at an unusually young age.

Methods

PATIENTS AND STUDY DESIGN

We recruited 60 consecutive young hypertensive patients referred to our hypertension clinic. We also recruited 30 older hypertensive controls. The premature hypertension group was defined as patients who presented before the age of 36 years (mean (SD) age, 28.0 (7.1) years; range 19–36 years), while those presenting at an older age were described as the middle aged hypertensive group (mean age 42.5 (4.8) years, range 37–52 years). Another group of 30 normal young controls of less than 36 years (age matched to the premature hypertension group) were also recruited (mean age 31.1 (4.0) years, range 23–38 years). There were 60 premature hypertensive patients, 30 normal controls, and 30 middle aged hypertensive patients.

Patients were considered to be hypertensive when their blood pressure was found to be above 140/90 mm Hg on at least three clinical readings, and later confirmed by ambulatory blood pressure monitoring.

We analysed male and female groups separately because of the sex differences in levels of excretion of cortisol.^{20–21}

All patients underwent routine clinical examination and investigation, including biochemistry, ECG, chest x ray, and 24 hour ambulatory blood pressure monitoring. Twenty four hour ambulatory monitoring in patients with suspected hypertension provides accurate and reproducible values of blood pressure, and the average blood pressure measurements thus derived correlate better with target organ damage than single or multiple clinic measurements.^{22–29} Ambulatory blood pressure monitoring was performed using previously validated monitors and processors (TM 2420–2020, A&D company, Tokyo, Japan).³⁰ Blood pressure measurements were taken every 15 minutes during the daytime and every 30 minutes during sleep. During the monitoring period patients were instructed to perform their normal daily routine activities.

Echocardiography, ultrasound of the kidneys, urography, iodine-123 meta-iodobenzylguanidine (MIBG) scanning, captopril renal scan, computed tomography, and

Table 3 Results of endocrine, blood pressure, and renal investigations in the three groups

	Normal controls	p Value (A)	Premature hypertensive	p Value (B)	Middle aged hypertensive
<i>Male patients</i>					
Cortisol metabolites (µg/day)	7270 (1788)	0.0001	13 332 (6472)	0.002	8315 (3565)
Androgen metabolites (µg/day)	2783 (750)	0.2	3801 (2015)	0.03	2392 (1373)
ABPM 24 h systolic (mm Hg)	116.2	< 0.0001	147.5	0.27	158.9
ABPM 24 h diastolic (mm Hg)	73.8	0.005	89.3	0.45	95.2
24 h urinary sodium (mmol)	147 (32)		124 (26)		167 (57)
24 h urinary potassium (mmol)	69 (27)		88 (14)		72 (22)
24 h urine volume (ml)	1746 (466)		1792 (629)		1668 (280)
<i>Female patients</i>					
Cortisol metabolites (µg/day)	4588 (1480)	< 0.0001	11 016 (4261)	0.02	7613 (2507)
Androgen metabolites (µg/day)	1687 (636)	0.002	2958 (1672)	0.0003	1373 (748)
ABPM 24 h systolic (mm Hg)	113.4	0.0002	148	0.52	142.5
ABPM 24 h diastolic (mm Hg)	70.7	< 0.0001	98.7	0.1	85
24 h urinary sodium (mmol)	142 (44)		132 (36)		148 (45)
24 h urinary potassium (mmol)	76 (21)		87 (18)		75 (15)
24 h urine volume (ml)	1702 (842)		1640 (603)		1689 (889)

Values are mean (SD).

(A), p value between normal controls and premature hypertensive patients; (B), p value between premature hypertensive and middle aged hypertensive patients.

ABPM, ambulatory blood pressure monitoring.

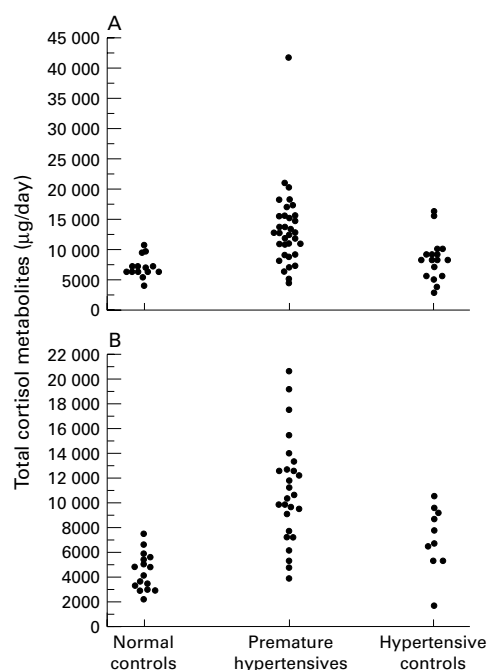


Figure 1 Twenty four hour urinary excretion of total cortisol metabolites in (A) male and (B) female patients.

magnetic resonance imaging of the adrenal glands, and estimation of 24 hour catecholamines were performed when clinically indicated.

Drug treatment in the hypertensive patients at the time of the investigation is summarised in table 1.

After excluding the patients with secondary hypertension, 24 hour urine was collected by all the patients in non-acid bottles to measure total cortisol and androgen metabolite excretion rates. Twenty four hour urinary cortisol measurements were performed by a gas chromatographic method,³¹ using a Hewlett-Packard gas chromatograph (5890 series II; Hewlett-Packard Inc, Andover, Massachusetts, USA), attached to a Hewlett-Packard mass selective detector.

The validity and reproducibility of the methods of measurements of 24 hour urinary cortisol metabolites have previously been demonstrated by our group.³² The coefficients of variation for cortisol metabolites in this study³¹ were from 2.4% to 16.6% (important metabolites—for example, androsterone, aetiocholanolone, dehydroepiandrosterone (DHA), and β -allo-tetrahydrocortisol—showed higher reproducibility). During the 24 hour ambulatory blood pressure monitoring and the 24 hour urine collection, and for 12 hours before, patients were asked to refrain from consuming excessive amounts of alcohol, tea or coffee.

STATISTICAL ANALYSIS

The data are presented as mean (SD). The results of individual values for total urinary cortisol metabolite and total urinary androgen metabolite excretion were considered abnormal if the values were greater than 2 SD above the mean of the normal controls. We used the Kruskal-Wallis non-parametric test to compare the three groups and the Mann-Whitney

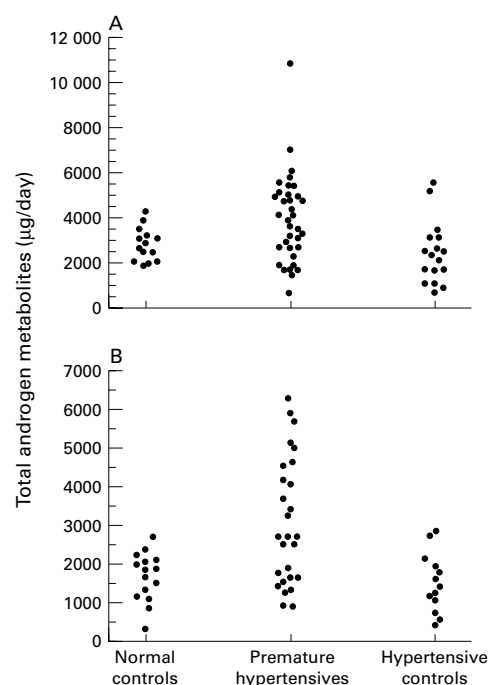


Figure 2 Twenty four hour urinary excretion of total androgen metabolites in (A) male and (B) female patients.

U test to assess the differences between two groups. Probability values of $p < 0.05$ were considered significant. Statistical analysis was performed using Statview 5.0 for Windows (Abacus Concepts, USA).

Results

There was no significant difference between three groups in body mass index (BMI), heart rate, or haemoglobin (table 2). The values for serum sodium and creatinine were within normal limits in all three groups. Serum potassium in the premature hypertension group was found to be significantly lower (mean (SD) 2.9 (0.8) mmol/l, $p = 0.001$) than in the other two groups. The premature hypertensive patients tended to have slightly lower blood pressure than the middle aged hypertensive patients, whether determined by 24 hour ambulatory blood pressure monitoring (table 3) or by clinic blood pressure (table 2).

TOTAL CORTISOL METABOLITES

The differences in total urinary cortisol metabolite excretion were highly significant ($p < 0.0001$) between the three groups in both male and female patients. Total urinary cortisol metabolites in the male subjects were substantially higher in premature hypertensive patients (13 332 µg/day) than in the middle aged hypertensive controls (8315 µg/day, $p = 0.002$) or the normal controls (7270 µg/day, $p = 0.0001$), as shown in fig 1A. In the female subjects there was an increase in urinary cortisol in the group with premature hypertension compared with the middle aged and young control groups (as shown in table 3 and fig 1B). Approximately two thirds of the male and female patients with premature hypertension had abnormally high urinary cortisol concentrations compared with the age matched

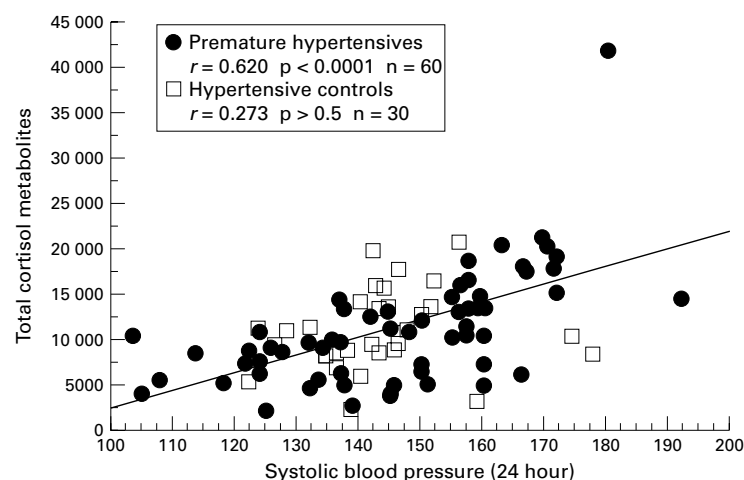


Figure 3 Regression analysis between total cortisol metabolites and systolic blood pressure in patients with premature hypertension and hypertensive controls.

normal controls (male patients 65% *v* 0%, $p = 0.001$; female patients 68% *v* 0%, $p = 0.0008$), or with the middle aged hypertensive group (male patients 65% *v* 0%, $p = 0.002$; female patients 65% *v* 20%, $p = 0.02$).

TOTAL ANDROGEN METABOLITES

In contrast to the male patients, among the female patients there was a significant difference in total urinary androgen metabolite excretion among the three groups ($p = 0.001$). In female patients, the total urinary androgen metabolite excretion was higher in the premature hypertensive group (2958 $\mu\text{g/day}$) than in the middle aged hypertensive group (1373 $\mu\text{g/day}$; $p = 0.0003$) or in the normal controls (1687 $\mu\text{g/day}$; $p = 0.002$), as shown in table 3 and fig 2B. In male patients, total urinary androgen metabolite concentrations were similar in the premature hypertension group and the young normal subjects ($p = 0.2$). However, there was a significant difference when the premature hypertensive patients were compared with the middle aged hypertensive patients ($p = 0.03$), as shown in fig 2A. Approximately one third of male patients and two thirds of female patients with premature hypertension had abnormally high urinary androgen concentrations compared with their male and female counterparts, both in the young control group (male patients 34% *v* 0%, $p = 0.07$; female patients 63% *v* 0%, $p = 0.002$) and in the middle aged hypertensive group (male patients 34% *v* 12.5%, $p = 0.38$; female patients 63% *v* 10%, $p = 0.008$).

CORRELATIONS

The correlations between systolic blood pressure and the urinary excretion of total cortisol

metabolites and androgen metabolites in premature hypertensive patients, hypertensive controls, and normal controls are shown in table 4 and fig 3. A significant correlation was found between total cortisol metabolites and total androgen metabolites in the premature hypertension group (male patients $r = 0.499$, $p = 0.009$; female patients $r = 0.388$, $p = 0.500$), but not in the hypertensive controls ($p > 0.5$).

Discussion

In this study we found a significantly higher urinary excretion of total cortisol metabolites in individuals with premature hypertension than in normal individuals of similar age, or in patients with hypertension presenting at a later age but with similar body size. These increased cortisol metabolite excretion rates were seen in both male and female subjects and occurred in more than half the patients in the premature hypertension group. The results were found to be essentially identical when also analysed by parametric methods.

In the urine steroid analyses none of our patients had evidence of corticosterone or deoxycorticosterone secreting tumours, biosynthetic defects (such as 17-hydroxylase or 11-hydroxylase deficiency), mineralocorticoid excess syndrome, or dexamethasone suppressible hyperaldosteronism (table 5).³³⁻³⁸ There was no difference in weight nor was there any concomitant pathology that might explain the differences in urinary excretion of glucocorticoid metabolites. While we have not controlled for lifestyle and psychological "stress," the urine collections were obtained under home conditions, and experiences from ambulatory blood pressure monitoring suggest that this avoids an alerting response in most individuals.

Of the various pathogenic mechanisms involved in the development of hypertension, three that are important in rare familial cases have recently received special attention because they may be relevant to milder forms of essential hypertension. These are glucocorticoid remediable hyperaldosteronism, hypertension with variations in angiotensin converting enzyme activity, and Liddle's syndrome.³⁹⁻⁴⁶ Increased urinary excretion of glucocorticoid metabolites in young hypertensive patients,⁴⁷ in the absence of any other clinical or laboratory stigmata of secondary hypertension, is likely to reflect differences in glucocorticoid production. One possible underlying mechanism is a partial resistance of glucocorticoid receptors to cortisol. Normally cortisol and androgens have different affinities for two different types of

Table 4 Correlations between total urinary steroid metabolites and systolic and diastolic blood pressure

	Premature hypertensive	Middle aged hypertensive	Normal control
Total urinary cortisol metabolites <i>v</i> :			
Systolic blood pressure (24 h)	$r = 0.620, p < 0.0001$	$r = 0.273, p > 0.5$	$r = 0.271, p = 0.14$
Diastolic blood pressure (24 h)	$r = 0.162, p = 0.2$	$r = 0.013, p = 0.9$	$r = 0.039, p = 0.8$
Total urinary androgen metabolites <i>v</i> :			
Systolic blood pressure (24 h)	$r = 0.350, p = 0.01$	$r = 0.297, p = 0.1$	$r = 0.178, p = 0.3$
Diastolic blood pressure (24 h)	$r = 0.040, p = 0.7$	$r = 0.281, p = 0.1$	$r = -0.151, p = 0.4$

Table 5 Other conditions with glucocorticoid metabolite abnormalities

Condition	Metabolic abnormality
Tumours	
Corticosterone secreting tumours	High concentrations of corticosterone
Deoxycorticosterone secreting tumours	High concentrations of deoxycorticosterone ³³
Biosynthetic defects	
17-Hydroxylase deficiency	High ratio of THF + α THF/THE; low 17-hydroxycorticosterone concentrations ³⁴
11-Hydroxylase deficiency	Little or no cortisol excretion ³⁵
Other conditions	
Cushing's disease	High serum cortisol levels; high excretion of urinary free cortisol ³⁶
Mineralocorticoid excess syndrome	F:E ratio increased (cortisol to cortisone ratio increased) ³⁷
Dexamethasone suppressible hyperaldosteronism	High urinary excretion of 18-hydroxycortisol metabolites ³⁸
Partial glucocorticoid resistance	Total cortisol metabolites are increased

F:E ratio, cortisol to cortisone ratio; THE, tetrahydrocortisone; THF, tetrahydrocortisol.

glucocorticoid receptor. With receptor resistance, feedback inhibition of the hypothalamic-pituitary axis is less effective, leading to an increased production of adrenocorticotrophic hormone which in turn causes an increased production and excessive excretion of glucocorticoid metabolites. Many of these glucocorticoid metabolites have mineralocorticoid-like effects, leading to an increased retention of sodium and water in the body.^{14 15 48-50}

Androgen metabolite excretion rates were abnormally high in female patients with premature hypertension, but in the male patients such a clear difference was not seen. It is possible that any tendency for premature hypertension to be associated with high androgen concentrations is masked by the higher background concentrations in male subjects.

Complete glucocorticoid receptor resistance is incompatible with life, because glucocorticoids have an important role in maintaining and regulating several vital mechanisms.⁵¹⁻⁵³ Partial glucocorticoid resistance, however, can occur^{15 50} and is a familial disease with clinical manifestations that may include high serum cortisol concentrations, increased 24 hour urinary free cortisol, hypertension, hypokalaemia, hirsutism, and fatigue. In a study of 33 blood relatives of an index father and son with partial glucocorticoid resistance, nine of 33 had hypertension. In another study of six patients with partial glucocorticoid resistance and increased circulating concentrations of cortisol and deoxycortisol, one was hypertensive at the age of 36. In the present study we evaluated 45 hypertensive patients under the age of 36 years and found that 65% of them had partial glucocorticoid resistance syndrome, with increased urinary excretion of cortisol metabolites.

CONCLUSIONS

We have identified a subset of young hypertensive patients with increased excretion of glucocorticoid metabolites in urine. This subset of individuals with premature hypertension may comprise a significant proportion of the young hypertensive population presenting to a tertiary hypertension clinic. We propose a syndrome of premature hypertension with increased urinary excretion of glucocorticoid metabolites, perhaps representing the effects of mild partial glucocorticoid resistance.

This study was presented as an abstract at the British Society of Cardiology in 2000.

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IMAGES IN CARDIOLOGY

Tricuspid valvectomy following tricuspid valve endocarditis on an intravenous drug addict

A 50 year old man was originally referred in 1983 with a nine week history of multiple complaints of headache, backache, profuse night sweats with rigors, anorexia, and general malaise. He was a registered intravenous drug abuser for many years, and had been recently prescribed methadone. On admission, he had a temperature of 38°C and a maculopapular rash over his arms and legs. He was jaundiced and anaemic with a haemoglobin concentration of 7.2 g/dl (4.47 mmol/l). His jugular venous pressure was raised at 4 cm above the clavicle with a prominent V wave. On auscultation the patient had a pansystolic murmur at the left sternal edge which was accentuated on inspiration. An echocardiogram showed massive vegetations on the tricuspid valve with severe tricuspid regurgitation. The diagnosis of infective endocarditis was made and confirmed with blood cultures positive for *Staphylococcus aureus* septicaemia. In November 1983 the patient underwent total valvectomy without insertion of an artificial valve because of the potential for further infections while he continued his rehabilitation. In 1985 he stopped all intravenous drug use. He remained well in New York Heart Association functional class I until 1997 when



he underwent cardioversion for atrial fibrillation. Despite an early success, the patient remained in controlled atrial fibrillation and is now under consideration for a tricuspid valve replacement.

The figure shows a transoesophageal view of the right ventricular inflow tract, where no tricuspid valve can be seen.

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